TEN-YEAR SURVIVAL OF PATIENTS WITH AIDS RECEIVING ANIRETROVIRAL THERAPY IN HAITI AND LESSONS LEARNED FROM THE SURVIVORS

A Thesis

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by

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ABSTRACT

Background: Long-term outcomes of antiretroviral therapy (ART) in resource-poor settings in Haiti are unknown. Understanding the psychosocial and contextual factors that enable patients living with HIV/AIDS to survive at least 10 years after the initiation of ART is necessary. Given Haiti's unique and fragile political and economic infrastructure, we describe the 10-year outcomes, characteristics of the first cohort of patients receiving ART in Haiti, and the experience of the 10-year survivors in the following chapters.

Methods: Data from 910 patients, age ≥ 13 years, who initiated ART from 2003-2004 were included. Lost-to follow-up (LTF) was defined as no clinic/pharmacy visit within 180 days of the date of censor. Kaplan Meier, contact tracing with inverse probability weighting, and multiple imputation methods were used to estimate survival. Cox modeling and logistic regression were used to identify characteristics associated with survival. Additionally, individual audiotaped in-depth interviews that lasted 45 to 60 minutes using a semi-structured open-ended format were conducted with 25 participants who survived at least 10 years with AIDS in between January 2015 and August 2015. Grounded theory approach was used for data collection and analysis. Each interview was then transcribed verbatim and back-translated from Creole to English. Questions focused on understanding how participants survived in the midst of challenges faced by the 10-year survivors since starting ART, coping strategies used to overcome those challenges, accomplishments that they made during those 10 years, and their hopes.

Results: Among 910 adults who initiated ART, 55% were female, median age was 38 years, and median CD4+ was 131 cells/uL (IQR 57-212). Ten years after ART initiation,

53% were alive, 27% dead, 12% were LTF, and 8% transferred care. Ten-year survival estimates ranged from 63–71%. Forty-two percent of deaths occurred in the first 6 months; characteristics associated with early death were being male, age > 50 years, low weight, WHO Stage III/IV, and baseline TB. Characteristics associated with death after 6 months were age > 50 years, income < $1 per day, low weight, and low adherence. Among 10-year survivors, 58% were female, median age was 49 years (IQR43-55), and median CD4+ was 541 cells/uL. Seventy-three percent remained on first-line therapy and 38% had a chronic non-communicable disease. We integrated our core findings into an explanatory framework. The 25 participants described stressors aside from HIV, including poverty, sociopolitical challenges and stigmatization that are counterbalanced with positive outlook and the fact of having a goal. Psychosocial factors like caring for one's child, spirituality and faith, the role of providers and adherence to antiretroviral helped them to look past the disease and have another meaning to theirs lives in order to survive the 10 years of ART.

Conclusion: The 10-year survival of patients with AIDS receiving ART in Haiti is approximately 70%, which demonstrates the long-term sustainability of international efforts to provide ART in resource-poor settings. Aside the devastating health impacts of HIV itself, there was an underlying current of resilience, hope, and the desire to live. As described in the second study, women with children wanted to work and support their children's education. This study provides a portrait of Haiti that is not defined by death or hopelessness.

BIOGRAPHICAL SKETCH

Samuel Pierre received his Doctorate of Medicine from the University of the State of Haiti, School of Medicine and Health Sciences, Port-au-Prince, Haiti in 2008. He completed his social service residency at St. Boniface Hospital, Fond-des Blancs, Haiti in 2009. Dr. Pierre is currently clinical investigator and primary care physician at the GHESKIO Center in Port-au-Prince, Haiti. Dr. Pierre's research focuses on HIV implementation science geared towards improving access and quality of care in Haiti. Dr. Pierre is interested in the long-term observation of HIV positive patients receiving antiretroviral therapy (ART), and the long-term benefits and clinical outcomes of patients who have undergone early ART treatment. Dr. Pierre has strong passion, and perspective for improving the health of impoverished communities in Haiti. Dr. Pierre's research is dedicated to pursuing population-level implementation research as it relates to retaining patients in medical care.

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While only my name appears on the cover of this thesis submission, many people have contributed to its production. I dedicate my gratitude to all those people who have made this thesis possible and because of whom my graduate experience has been one that I will cherish forever.

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My co-mentor, Dr. Daniel Fitzgerald, has been always there to listen and give advice. I am deeply grateful to him for the long discussions that helped me sort out the technical details of my work. Dan taught me how to question my thoughts and express my ideas. His patience and support helped me overcome many crisis situations and finish this thesis. I hope that one day I will become as good a mentor to my students as Dan has been to me.

My co-mentor, Dr. Carla Boutin-Foster, is one of the best teachers that I have had in my life. Her passion for qualitative research sets high standards for me as a student and she encourages and guides me to meet those standards. She oriented me to qualitative research and framed my work, "Lessons learned from ten-year AIDS survivors." I am indebted to her for her continuous encouragement and guidance.

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I would like to acknowledge all the 10-year AIDS survivors whom my work is based on. The 25 who I interviewed help me understand the need of the AIDS patients, which is not only limited to antiretroviral therapy and care, but also social support. I really appreciate the resilience of these patients.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER ONE

TEN-YEAR SURVIVAL OF PATIENTS WITH AIDS RECEIVING ANIRETROVIRAL THERAPY IN HAITI

ABSTRACT

Background: Long-term outcomes of antiretroviral therapy (ART) in resource-poor settings are unknown. We describe the 10-year outcomes and characteristics of the first cohort of patients receiving ART in Haiti.

Methods: Data from 910 patients, age ≥ 13 years, who initiated ART from 2003-2004 were included. Lost-to follow-up (LTF) was defined as no clinic/pharmacy visits within 180 days of the date of censor. Kaplan Meier, contact tracing with inverse probability weighting, and multiple imputation methods were used to estimate survival. Cox modeling and logistic regression were used to identify characteristics associated with survival.

Results: Among 910 adults who initiated ART, 55% were female, median age was 38 years, and median CD4+ was 131 cells/uL (IQR 57-212). Ten years after ART initiation, 53% were alive, 27% dead, 12% were LTF, and 8% transferred care. Ten-year survival estimates ranged from 63–71%. Forty-two percent of deaths occurred in the first 6 months; characteristics associated with early death were being male, age > 50 years, low weight, WHO Stage III/IV, and baseline TB. Characteristics associated with death after 6 months were age > 50 years, income < $1 per day, low weight, and low adherence. Among 10-year survivors, 58% were female, median age was 49 years (IQR43-55), and median CD4+ was 541 cells/uL. Seventy-three percent remained on first-line therapy and 38% had a chronic non-communicable disease.

Conclusion: The 10-year survival of patients with AIDS receiving ART in Haiti is approximately 70%, which demonstrates the long-term sustainability of international efforts to provide ART in resource-poor settings.

INTRODUCTION

Over the past decade, nearly 12 million HIV infected persons have initiated antiretroviral therapy (ART) in resource-poor countries (1, 2). This extraordinary international effort has led to a decrease in HIV-related deaths from 2.3 million in 2005 to 1.6 million in 2012, and a decrease of HIV transmission at the population level (1). Scale-up of ART has also dramatically strengthened families and communities through increased school attendance, increased worker productivity, and improved family income status (3-6).

The long-term, 10-year survival of HIV-infected persons receiving ART in resource-poor countries remains uncertain. Long-term survival estimates are important to evaluate the impact and sustainability of HIV programs, identify the health needs of patients on lifelong treatment, and adapt HIV programs to meet the needs of this aging population.

The clinic of Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) was established in 1983, is the first HIV/AIDS clinic in Latin America and the Caribbean (7). In 2003, Haiti had an adult HIV prevalence of 6%, which was the highest in the Western Hemisphere (8). From 2003 to 2004, GHESKIO obtained international funding and was one of the first organizations to provide free ART to all eligible patients in a resource-poor setting (7). The objectives of this analysis are to determine the 10-year survival of the first cohort of patients to receive ART in Haiti, identify predictors associated with survival, and detail the characteristics of the 10-year survivors.

METHODS

Study Site and Population:

GHESKIO is located in downtown Port-au-Prince and serves a catchment population of approximately 3 million persons, the majority of whom live under the national extreme poverty line of 1.24 dollar per day (9). The study population is the first cohort of 910 individuals, age 13 years or older, who initiated ART at GHESKIO between March 2003 and April 2004. Details and short-term outcomes of this cohort have been previously described (7, 10).

GHESKIO's ART Program:

The GHESKIO clinic staff who initiated and cared for the cohort of patients during the study period (2003-2014) was compromised of a multidisciplinary team of physicians, nurses, a social worker, peer counselors and community health workers. Patients were routinely seen in the clinic by a physician every 2 weeks during the first 3 months of treatment and by a nurse monthly thereafter. Eligibility criteria for ART in 2003-2004 followed WHO guidelines and included an AIDS-defining illness or a CD4 count < 200 cells/uL(11). In 2006, eligibility criteria for ART changed to a CD4 count < 350 cells/uL and in 2010 again changed to a CD4 count < 500 cells/uL in 2010(12, 13). From 2003 to 2004, the first-line ART regimen was zidovudine, lamivudine, and efavirenz or nevirapine, with single-drug substitutions permitted as outlined by WHO. Tenofovir-based regimens became first-line treatment in 2010. Second-line regimens (lopinavir and atazanavir) were available in 2004. Medications were dispensed monthly directly to the patients. CD4 counts were performed every 6 months and viral load was not routinely measured. Retention in care and adherence to therapy was encouraged by peer counseling by people with AIDS, transport support, home visits, and social support programs. Patients who missed a clinic appointment were traced in

the community by field workers, for up to 6 months from the date of the missed appointment to ascertain vital status and return patients to care. Since 2003, over 10,000 patients have been initiated on ART at GHESKIO.

Clinical Measurements and Outcomes:

Clinical measurements at the time of ART initiation included body weight, CD4 count, co-infection with tuberculosis, and WHO staging. Demographic characteristics included age, sex, income (dichotomized at $1/day), marital status, residence, referral type for HIV care, and education.

The primary outcome of this analysis was survival at 10 years after initiation of ART. Date of death and transfer were documented in the medical record. A patient was categorized as lost to follow-up (LTF) if there was no clinic or pharmacy visit within 180 days of the last clinic visit or the 10-year anniversary date of ART initiation. We examined survival estimates both after the first 6 months of ART and at 10 years based on studies reporting high rates of early mortality immediately after ART initiation due to opportunistic infections (10, 14-17).

Adherence, measured at 6 months after ART initiation, was defined as the proportion of pills prescribed that patients collected from the pharmacy (18). Diagnosis of tuberculosis followed the definition of the American Thoracic Society and has been used in our prior reports (19-23). Diagnosis of a chronic non-communicable disease was assessed by identifying a clinical diagnosis in the medical or pharmacy record of cardiovascular disease (e.g., hypertension, coronary artery disease, or hyperlipidemia), chronic lung disease (e.g, asthma and chronic obstructive lung disease), or diabetes.

Contact Tracing of Patients Lost to Follow-up:

GHESKIO staff routinely traced patients who missed appointments throughout the study period. In 2013-2014, staff attempted to contact all patients who had been categorized as LTF at 10 years after initiating ART, the end of the study period.

Events in Haiti Over the 10-Year Follow Up Period:

During the 10-year study period, there were continuous political, socioeconomic and natural catastrophes in Haiti (24). In 2004, there was a political coup resulting in UN military occupation of the country with a series of disputed political elections. A historic earthquake occurred in Port-au-Prince in January 2010, which killed over 200,000 and displaced more than 3 million (25). The largest Cholera epidemic in modern history hit in October 2010 and claimed an additional 8,500 lives (26).

Statistical Analysis:

We used three methods to assess survival at 6 months and 10 years of follow-up: 1) Kaplan-Meier survival analysis methods, 2) inverse-probability weighting survival analysis, and 3) logistic regression with the use of multiple imputation with chained equations. Each method accounts for LTF differently given the status of LTF is not a patient outcome but rather a mixed category of undocumented deaths, undocumented or silent transfers, and patients who are alive but disengaged from care (27-29). Standard Kaplan Meier survival methods censor patients who are LTF, which assumes that being LTF is not associated with survival. Patients who were LTF or transferred were censored at the date of last clinic date of date of transfer. Survival analysis with inverse probability weighting assigns a weight equal to the inverse probability of vital status ascertainment for traced participants (30). Applying these weights, participants

traced are weighted to represent the population of all patients who were lost to follow-up. The weighting assumes that individuals successfully traced at 10 years have the same probability of death as those LTF but not traced throughout the study period. This method assumes that the sample with successful tracing is representative of those LTF who were not successfully traced. The third method is logistic regression with the use of multiple imputation with chained equations (20 imputations) to assign vital status at 6 months and 10 years (31). Multiple imputation techniques assume that missing data is missing at random and that, conditioned on the covariates used to impute outcome status, individuals who are LTF have the same risk of an outcome (in this case death) as individuals not LTF. Using this method, vital status was imputed among participants categorized as LTF or transferred.

Characteristics associated early and late death were generated using cox proportional hazard models and logistic regression. Missing data for CD4+ count, weight, and adherence at 6 months were imputed. Variables associated with mortality in previous publications or in our clinical experience were included in the initial model. We used STATA statistical software (Version 13.0, College Station, Tx) for all analyses.

Ethics:

The institutional review boards at GHESKIO and at Weill Medical College of Cornell University approved this study.

RESULTS

Patient Characteristics at ART initiation:

Table 1.1 describes the characteristics of the 910 patients who were initiated on ART

in 2003–2004. Fifty-five percent were female with a median age of 38 years (IQR 33-45). Approximately half of the cohort lived in extreme poverty earning < $1 per day, and had no or only primary-level schooling. All patients had AIDS at the time of ART initiation: median CD4 count was 131 cells/uL (IQR 51-212) with 20% having a CD4+ < 50 cells/uL, and 39% with advanced WHO Stage III or IV symptoms.

Table 1.1 Characteristics of Patients at Time of ART Initiation in 2003–2004 (N=910)

DEMOGRAPHIC CHARACTERISTIC	**N (%)**
Female	504 (55)
Age (years)	
Median (IQR) (range)	38 (33, 45) (13–68)
13-17	18 (2)
18-24	40 (4)
25-50	752 (83)
>50	100 (11)
Income < $1 per	513 (56)
Resident of Port-au-Prince Province	414 (90)
Self-referred for HIV testing	419 (46)
Education, highest level	
None	157 (17)
Primary School	281 (31)
Secondary School	404 (44)
College	68 (8)
Marital Status	
Married (including common law)	447 (49)
Separated	159 (18)
Single	209 (23)
Widowed	95 (10)
CLINICAL CHARACTERISTIC	
Body weight (kg) by gender	
Men, median(IQR)	54 (46, 61)
Women, median (IQR)	40 (47, 54)
Missing	23 (3)
CD4+ count (cells/uL)	
Median (IQR) (range)	131 (51,-212) (0–1400)
<50	179 (20)
51-250	510 (56)
251-350	70 (8)
>350	42 (5)
Missing	109 (12)
WHO Stage III or IV symptoms	358 (39)
Tuberculosis at baseline	80 (9)
Initial ART regimen (Zidovudine, Lamivudine, Efavirenz or Nevirapine)	810 (89)

Patient outcomes:

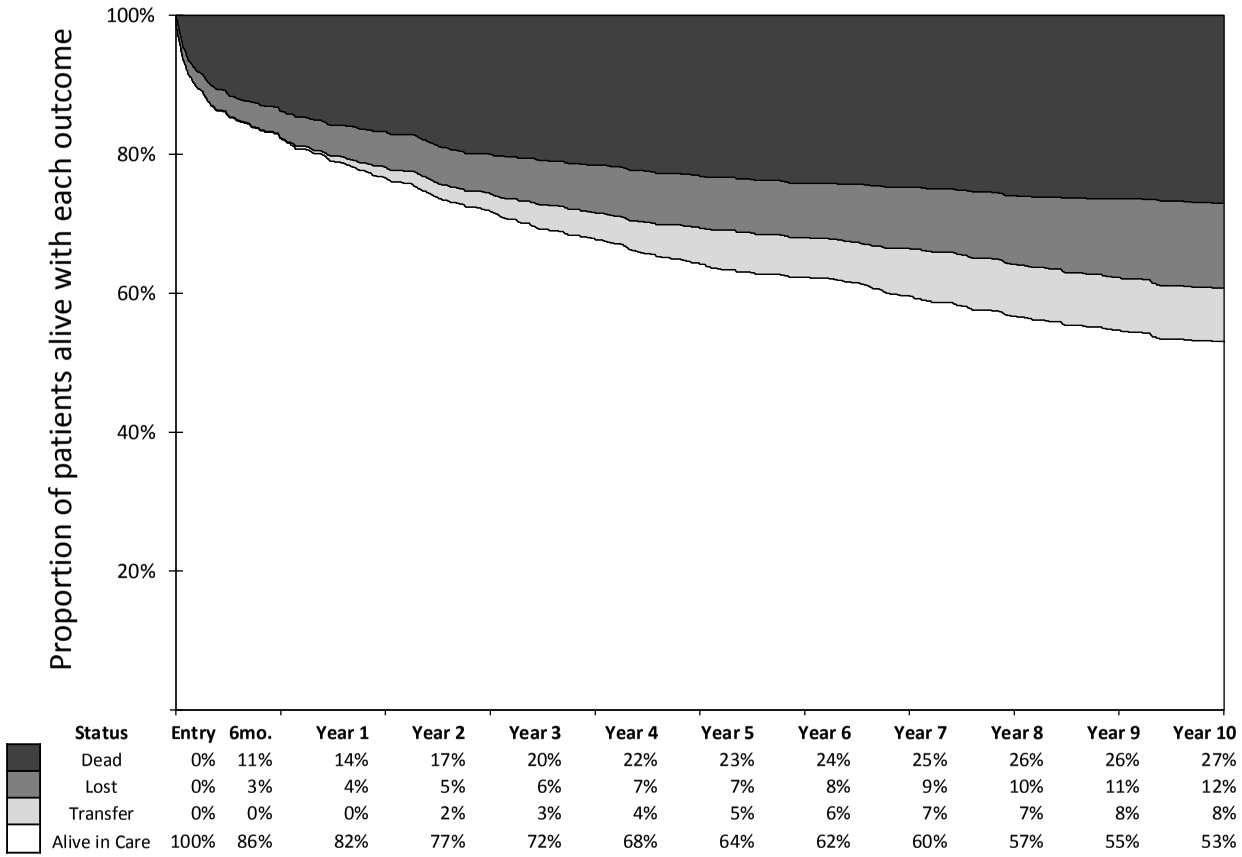
Contact tracing of 161 participants who were categorized as LTF at the end of the 10-year study period found 39 patients to be alive and re-engaged in care, 11 dead, and the remaining 111 were classified as lost.

Six Months: At 6 months after ART initiation, 779 (86%) of the cohort was alive, 103 (11%) were dead, 27 (3%) were lost and one patient transferred (**Figure 1.1**).

Ten Years: At 10 years after ART initiation, 482 (53%) were known alive, 246 (27%) were dead, 111 (12%) were lost, and 71 (8%) had transferred.

The mortality rate in the first 6 months was 25 deaths per 100 patient years (PY). Over the next 9.5 years the mortality rate was 2.5 deaths per 100 PY. Mortality rates did not significantly differ in calendar year 2010, following the earthquake as compared to other years (1 death/100 PY in 2009, 2 deaths/100 PY in 2010 and 1.5 deaths/100 PY in 2011).

Figure 1.1 Outcomes over 10 years of follow-up among 910 patients who initiated ART between 2003–2004 in Haiti

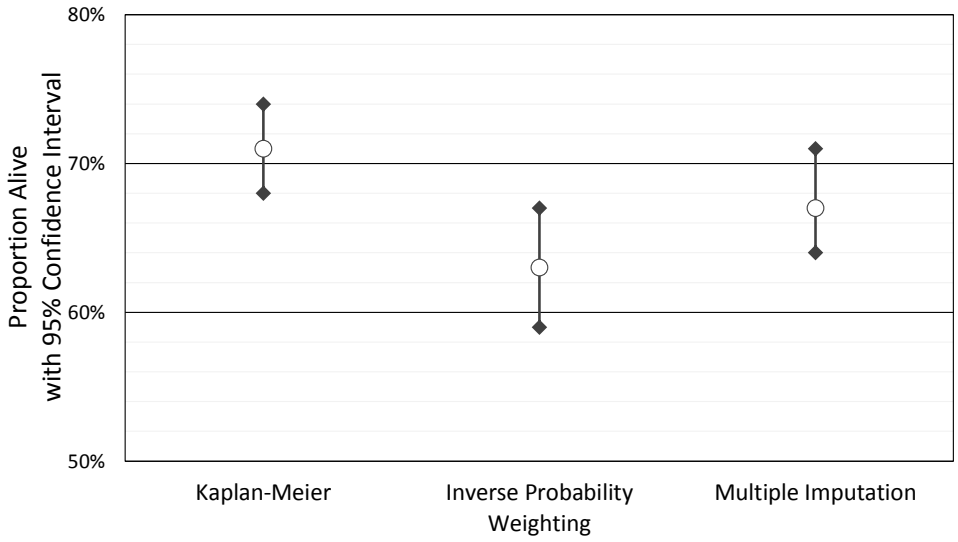


Status	Entry	6mo.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Dead	0%	11%	14%	17%	20%	22%	23%	24%	25%	26%	26%	27%
Lost	0%	3%	4%	5%	6%	7%	7%	8%	9%	10%	11%	12%
Transfer	0%	0%	0%	2%	3%	4%	5%	6%	7%	7%	8%	8%
Alive in Care	100%	86%	82%	77%	72%	68%	64%	62%	60%	57%	55%	53%

Figure 1.1 Outcomes over 10 years of follow-up among 910 patients who initiated ART between 2003–2004 in Haiti

Ten-Year Survival Estimates: Three methods were used to estimate survival by accounting for death among patients categorized as lost to follow up. Kaplan Meier survival analyses estimated that 71% (95% CI 68%–74%) were alive at 10 years. Inverse probability weighting estimated 63% survival (95% CI 59%–67%), and multiple imputation methods estimated 67% survival at 10 years (95% CI 64%–71%) (**Table 1.2**).

Table 1.2 10-year Survival Estimates using three survival analysis methods for 910 patients who initiated ART between 2003-2004 in Haiti



METHOD	ESTIMATED ALIVE, % (95% CI)
Kaplan–Meier	71% (68, 74)
Inverse Probability Weighting	63% (59, 67)
Multiple Imputation	67 (64, 71)

Tuberculosis: Eighty patients (9%) had tuberculosis at time of ART initiation. A total of 134 patients (15%) developed tuberculosis over the study period with TB incidence of 14.5 cases/100 PY in the first 6 months and 1.3 cases/100 PY from 6 months to 10 years.

Adherence: Among patients who survived to 6 months, the median adherence was 97% (IQR 88%-100%). Sixty-nine percent had an adherence greater than 90%, 11% had adherence 80-80%, 6% had adherence 70-79%, and 15% had adherence less than 70%.

Predictors of Survival:

The characteristics predictive of 6 month mortality were predominately biomedical factors including low weight, WHO Stage III/IV symptoms and baseline TB. Other predictors include being male and age > 50 years (**Table 1.3**). Characteristics associated with death after 6 months through 10 years include age > 50 years and lowest quartile weight for sex, with the addition of sociodemographic and behavioral characteristics of extreme poverty and lowest quartile of adherence (**Table 1.3**). Using logistic regression with multiple imputations of outcome status produced similar results (**Appendix Table 1.1**).

Table 1.3 Characteristics associated with death among 910 patients who initiated ART in Haiti in 2003-2004 using Cox Proportional Hazard Modeling.

Table 1.3 Characteristics associated with death among 910 patients who initiated ART in Haiti in 2003-2004 using Cox Proportional Hazard Modeling.

	From 0 to 6months		From 6 months to 10 years	
	Dead		Dead	
Predictor	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**
Female	0.77 (0.52-1.13)	**0.50 (0.31-0.81)^**	0.91 (0.65-1.27)	0.75 (0.52-1.08)
Age				
13-24	1.00 (0.44-2.29)	0.68 (0.29-1.63)	**2.48 (1.46-4.21)^**	1.76 (0.98-3.17)
25-50	Referent	Referent	Referent	Referent
> 50	1.44 (0.86-2.40)	**2.01(1.18-3.42)^**	**2.11(1.39-3.19)^**	**2.41 (1.57-3.70)^**
Resident of Port-au-Prince	1.11 (0.74-1.66)	1.15 (0.76-1.73)	1.15 (0.82-1.62)	1.18 (0.84-1.67)
Self-referred	Not included	Not included	1.33 (0.96-1.85)	1.39 (0.99-1.96)
Income <$1/ day	**1.51 (1.01-2.27)^**	1.40 (0.91-2.16)	**1.68 (1.19-2.37)^**	**1.54 (1.06-2.24)^**
Weight by sex				
Lowest quartile	**2.34 (1.54-3.55)^**	**2.42 (1.41-4.17)^**	**1.78 (1.23-2.58)^**	**1.68 (1.08-2.60)^**
Quartile 2-4	Referent	Referent	Referent	Referent
CD4+ at ART initiation				
<50	**6.91 (1.06-45.22)^**	5.78 (0.87-38.29)	1.18 (0.43-3.23)	1.48 (0.53-4.14)
51-250	2.97 (0.46-19.22)	3.21 (0.49-20.96)	1.32 (0.52-3.36)	1.65 (0.64-4.24)
251-350	2.81 (0.40-19.84)	3.59 (0.51-25.23)	1.86 (0.67-5.20)	2.18 (0.76-6.25)
>350	Referent	Referent	Referent	Referent
WHO Stage at ART Initiation				
WHO I / II	Referent	Referent	Referent	Referent
WHO III/IV	**4.16 (2.72-6.36)^**	**3.30 (2.11-5.15)^**	1.28 (0.91-1.79)	1.18 (0.82-1.69)
Baseline TB	**2.40 (1.44-3.99)^**	**1.92 (1.13-3.27)^**	1.57 (0.93-2.63)	1.63 (0.95-2.77)
Incident TB (0-6 months)			1.74 (0.96-3.14)	1.39 (0.74-2.58)
Adherence (0-6 month)				
Lowest quartile			**2.96 (1.81-4.83)^**	**2.80 (1.69-4.64)^**
Quartile 2-4	Referent	Referent	Referent	Referent

Cox Proportional Hazard models using the MI data Weight, CD4+ and adherence were imputed if missing

**Adjusted for sex, age, residency, referral type, weight, CD4 HIV stage, TB and adherence*

^ p value ≤ 0.05

Characteristics of the 10-Year Survivors:

The median age of survivors was 49 years (IQR 43-55). Median body weight increased by 2 kilograms for men (from 58 to 60kg) and by 9 kg for women (from 51 to 60 kg) from time of ART initiation to 10 years. Median CD4 count increased from 146 cells/uL (IQR 62-214) at time of ART initiation to 541 cells/uL (IQR 355-762) at 10 years. Over two-thirds of patients (73%) remained on first-line regimens over the 10-year period. The median time to switch among those on second-line was approximately 6 years (75 months (IQR 46-106). Over a third of survivors (36%) had documented evidence of a chronic non-communicable disease, most often cardiovascular disease (109), lung disease (67), and diabetes (2). Four patients had more than one diagnosis.

DISCUSSION

This analysis documents the 10-year survival of the first cohort of adult and adolescent patients to receive ART in a public HIV program in Haiti to be 63-71%. Such high survival is impressive given a large proportion of the cohort had advanced AIDS at time of ART initiation and the continuous political, socioeconomic and natural catastrophes that occurred in Haiti during the 10-year study period. These results demonstrate the long-term sustainability of international efforts to provide ART in resource-poor settings and the effectiveness of ART on patient outcomes.

Ten-year survival of ART cohorts from resource-poor settings remain uncertain. Three-year retention after ART initiation has been reported to be 64% in Latin America and the Caribbean, 65% in Africa, and 80% in Asia in a recent systematic review of 154 cohorts from 42 low- and middle-income countries (32). In this same review, estimated retention across all sites using lifetime table analysis was

60% at 5 years. Long-term survival of our cohort appears similar to the early ART era in the United States, defined as 1997-1999, which report annual death rates of 2.8% to 4.1% (33). Our cohort's 10-year survival estimates of approximately 70% illustrate what is possible in resource-poor settings.

The high mortality seen in the 6 months immediately after ART initiation is similar to other studies (14, 34-39) and in part reflects the high burden of opportunistic infections (10, 14-17). The early mortality in this cohort is similar to early mortality rates from other ART programs in resource-poor settings (14, 34-38). A meta-analyses of one-year mortality was 6.4% (95% CI 5.1%-7.7%) across 18 ART programs in Africa, Asia, and South America and 8.3% (95% CI 7.6% -9.1%) from 7 sites in Latin America and the Caribbean (40) (41). In these programs, the proportion of patients who were categorized as LTF was greater than those with documented death. Given a non-trivial proportion of the patients who are categorized as LTF represent undocumented death (42, 43), corrected death rates from these programs are much higher. Interestingly, there does not appear to be an increase in the rate of death or LTF in our cohort during 2010 and 2011, post-earthquake.

Characteristics associated with early death in this cohort are consistent with those in the literature including male sex, older age, advanced WHO stage, low weight, and tuberculosis (34, 39, 44-49). Like other cohorts, advanced age remains an independent risk factor for early and late death, and may underscore data suggesting younger age favors CD4+ cell restoration on ART (48, 50, 51). Characteristics associated death after 6 months to 10 years shift from biomedical characteristics to demographic and behavioral characteristics. Specifically, extreme poverty of earning less than $1 per day and lowest quartile adherence became significant predictors.

A striking characteristic of the survivors is the fact that 73% remain on first-line therapy after 10 years. In a prior study from Haiti, patients who failed first-line therapy based on clinical and/or immunologic criteria and did not switch to second-line therapy faced a higher mortality than those who switched after failure (52). Perhaps, one reason we are seeing such high proportion of first-line therapy among the 10-year survivors is that patients who failed first-line died prior to switching to second-line. New initiatives to monitor viral load annually among ART patients may identify patients earlier who qualify for second-line therapy and further improve survival.

Increasing prevalence of chronic non-communicable diseases (NCDs) among populations on long-term ART is well documented and is due to a convergence of factors from the virus, treatment side-effects, and host responses leading to metabolic abnormalities (53, 54). The prevalence of NCDs among survivors (38%) may differ from cohorts who initiate treatment at higher CD4 counts in the past several years. Cardiovascular and lung diseases have been associated with low CD4 counts (55-59) and our cohort had very low CD4 counts at ART initiation when ART eligibility was based on a CD4+ count < 200 cells/uL. Additionally, zidovudine— for which 89% of patients were using for first-line treatment— and stavudine are associated with metabolic diseases after adjustment for risk factors for diabetes and lipids (60), and current first-line regimens do not include these medications. The prevalence of NCDs among survivors in this cohort draws attention to importance of NCD diagnoses and management among persons living with HIV in resource-poor settings (61). Providers of HIV care among aging HIV populations will need to be trained in NCD management and integrated models of HIV-NCD care need to be implemented.

Strengths of this analysis include it is one of the first large cohorts of patients to initiate ART in a resource-poor setting, and reports 10-year survival. The inclusion of multiple methods to estimate and compare survival and that fact that only 12% of patients were lost over the 10-year period provides confidence around the survival estimate.

CONCLUSION

The 10-year survival of patients with AIDS receiving ART in Haiti is approximately 70%, which demonstrates the long-term sustainability of international efforts to provide ART in resource-poor settings. These results attest to the collaboration of international donors and the Haitian Ministry of Health, the dedication of Haitian clinic staff, and the perseverance of patients all of which have transformed HIV into a chronic manageable disease.

APPENDIX 1

Appendix Table 1.1 Predictors of survival at 6 months and 10 years using logistic regression model and survival estimated by multiple imputation methods.

Predictors of 6-month mortality	**OR**	**P Value**
Advanced stage (WHO III or IV)	3.2	<0.001
Tuberculosis (present at baseline)	1.9	0.04
Weight (for every -10kg difference from median weight for gender)	1.5	0.002
CD4+ (for every lnCD4 difference of 0.7 = difference between 200 and 100, or 100 and 50)	1.2	0.007
Area under ROC curve = 0.75		
Predictors of 10-year mortality		
Adherence (for every -10 percentage point difference)	1.8	<0.001
Income < $1 per day	1.6	0.007
Age (for every +15-year difference)	1.6	<0.001
Advanced stage (WHO III or IV)	1.6	0.01
Weight (for every -10kg difference from median weight for gender)	1.3	0.004
Area under ROC curve = 0.80		

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CHAPTER TWO

LESSONS LEARNED FROM THE TEN YEAR AIDS SURVIVORS AT GHESKIO

ABSTRACT

Introduction: The excellent 10-year survival of the first cohort of AIDS patient who initiated ART at GHESKIO are comparable to that observed in other countries in which ART has been initiated. However, given Haiti's unique and fragile political and economic infrastructure these result deserve special attention. While few studies detail the experiences of those who have experienced long-term survival after starting ART, this study provides a unique opportunity to understand the psychosocial and contextual factors that enable patients living with HIV/AID to survive at least 10 years at GHESKIO after the initiation of ART.

Methods: Individual audiotaped in-depth interviews that lasted 45 to 60 minutes, using a semi-structured open-ended format were conducted with 25 participants in between January 2015 and August 2015, who survived at least 10 years with AIDS. Grounded theory approach was used for data collection and analysis of this study. Each has then transcribed verbatim and back-translated from Creole to English. Questions focused understanding how they survived in the midst of challenges faced by the 10 year survivors since starting ART, coping strategies used to overcome those challenges, accomplishments that they made during those ten years, and their hopes.

Results: We integrated our core finding into an explanatory framework. Participants described stressors which is not only HIV but also poverty, sociopolitical challenges and stigmatization that are counterbalanced with positive outlook and the fact of having a goal. Psychosocial factors like caring for one's child, spirituality and faith, the role of providers and adherence to antiretroviral helped them to look past the disease and have another meaning to theirs lives in order to survive the 10 years of ART

Conclusion: Aside the devastating health impacts of HIV itself, there was an underlying current of resilience, hope, and the desire to live. The large proportion of women who have low education in Haiti does not necessarily equate with a lack of goals. As described in this study, women with children wanted to work and support their children's education. This study provides a portrait of Haiti that is not defined by death or hopelessness.

INTRODUCTION

Among Caribbean countries, Haiti is known to have one of highest prevalence rates of HIV.[1,2] In the early 1990s, prevalence rates peaked at 9% in some parts of the country. The compounding effects of abject poverty, limited educational opportunities, high unemployment rates, and several devastating natural disasters cannot be discounted. However, over the past decade, a dramatic shift was observed in HIV trends. This downward trend has been attributed to concerted and strategic efforts of the local health ministry, community-based organizations, faith-based organizations and NGOs such as the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections (GHESKIO).[4,5] GHESKIO, formed in 1982 by a group of Haitian health professionals, integrates HIV care with education on sexually transmitted infections, nutritional support, and economic development.[6] Research is also a core component of GHESKIO's mission.[7]

In 2003, GHESKIO initiated clinical trials of ART treatment which subsequently became standard of care that was rendered free-of-charge to all patients with AIDS. The advent of ART therapy in Haiti ushered in a new era of HIV treatment with unprecedented rates of survival. Prior to the initiation of ART, the one year survival was 30% which, improved almost 3-fold after the initiation of ART. The one-year survival rate among 910 adults and adolescent ART-naive patients who were

consecutively treated with ART from March 2003 to May 2004 was found to be 87%. [8] Ten-year survival for this cohort was approximately 60% to 70%.[9] While these rates are comparable to that observed in other countries in which ART has been initiated, the rates in Haiti deserve special attention given Haiti's unique and fragile political and economic infrastructure. These rates of survival must be viewed in the context of the limited access to care, food insecurity, and tenuous housing. Surviving HIV under these conditions is a feat that is understated. Yet, much of the focus on HIV in Haiti remains on the staggering death rates. While this is understandable, the new trends in HIV outcomes also calls for a focus on the factors which enabled individuals to survive 10 years are unknown.

With few exceptions, the number of studies detailing the experiences of those who have experienced long-term survival after starting ART is limited.[10] Survival in the midst of political unrest, economic turmoil, and one of the most devastating earthquakes in the western hemisphere points to the resilience of the Haitian population. This study provides a unique opportunity to understand the psychosocial and contextual factors that enable patients living with HIV/AID to survive at least 10 years at GHESKIO after the initiation of ART. The study was conducted in Creole and therefore, provides lessons on cross-language approaches to conducting qualitative research. Understanding lived experiences of long-term survivors can be invaluable in developing interventions that are more responsive to the needs of patients.

METHODS

This qualitative study is nested within a larger study looking at cumulative incidence of survival at 10 years. The methods to ascertain survival have been described above and elsewhere in the literature.[9] Of the 910 Patients who initiated

antiretroviral therapy from 2003 through 2004 at GHESKIO, 482 patients (53%) were alive, 246 (27%) were deceased, 111 (12%) were lost to follow-up, and 71 (8%) had transferred to another clinic. This subsequent qualitative study is a follow up of 16 patients from this surviving cohort and nine 10-year survivors form a bigger 10-year survivor cohort.

Participants were patients who received care at GHESKIO. Given the stigmatization associated with HIV, this study utilized an exhaustive informed consent process that has been developed by researchers at GHESKIO. Careful steps were taken to ensure that all participants understood the rationale for the study and understood the reason for their participation. Participants were asked to complete a questionnaire detailing information about the study as a means of assuring the participants understood the objectives of the study and their role in the study. This process was conducted by social workers and field workers at GHESKIO.

Data Collection:

Grounded theory approach was used for data collection and analysis of this study. Grounded theory is an iterative process and evolving theory in the context of existing data until no new findings emerge (Charmaz, 2001). Individual in-depth interviews using a semi-structured open-ended format were conducted with participants between January 2015 and August 2015. All the interviews were conducted by the investigator in a private office at the GHESKIO. Interviews lasted about 45 to 60 minutes and each was audio-taped then transcribed verbatim. Questions focused understanding how they survived in the midst of challenges faced by the 10-year survivors since starting ART, coping strategies used to overcome those challenges, accomplishments that they made during those 10 years, and their hopes.

The interviews were all conducted by investigators who have received formal training in qualitative research as part of a Master of Science in Clinical Epidemiology and Health Services Research program. The training involved 6 weeks of didactic course work on the history and basic tenets of qualitative research as well as course work in qualitative data analysis. In addition, interviewers had opportunity to practice qualitative interviewing skills through role play with other students in the class. Additionally, guidance for the study design and interviews was provided by the senior author who is an expert in socio-behavioral research with more than a decade of experience performing qualitative research. The study was reviewed by GHESKIO IRB and the Cornell University IRB which approved the study. All study participants have provided written informed consent.

Data Analysis:

Grounded theory was used as the mean of understanding how the AIDS patients survived the 10 years of ART^{-1}. Data analysis occurred concurrently with data collection. Each interview was analyzed separately and as new questions arose about the underlying meaning of responses, new questions were added to further probes participants. As an example, initial interviews pointed to the salience of spirituality in the lives of participants. Therefore, new items were developed to further explore the role of spirituality and how it enabled survival. Additional probes included, “tell me about the role that church has play in your health," and "how has this supported or hindered you to remain healthy.” When respondents explicitly mentioned God, this was further probed with questions such as, “tell me more about how God has impacted your health."

As an inductive analytic approach, grounded theory involves constant comparison of data through a series of iterative steps to develop an inductively

derived theory from the data[11,12]. These steps involve include the identification of codes, concepts, categories and then theories to that describe the social phenomena of interest [13]. Codes are descriptive labels or tags that represent key concepts that are being conveyed in the data. Codes can be actual responses or in vivo codes, select words from the transcripts, or words that represent key concepts. The codes were then grouped into categories. Categories were then analyzed to identify recurring and dominant themes. This process is iterative and involves exploring new evolving data in the context of existing data until no new findings emerge. Detailed notes were maintained on the transcriptions, thus creating and 'audit trial' allowing for two separate and independent analyses of data. These data underwent two rounds of independent analysis or coding to insure trustworthiness.

Unique to this study was its cross-language and cross cultural focus. The primary language of participants and the study principal investigator was Creole. Creole has many idioms and nuances that may confer certain meanings that when translated to English, may lose the underlying meaning. Maintaining the meaning of responses as close as possible to what the participants intended is a core principle of qualitative research. [14]

The procedures for data analysis were done in both Creole and English following recommendation from the literature reviews. [15] All interviews were conducted by bilingual qualitative researchers in Creole the primary language of the participants. The first stage involved translating the Creole text into English. Content analysis coding, development of categories and themes were done in Creole and English independently by two bilingual qualitative researchers each independently deriving codes, categories, and themes in Creole and English. The Creole codes, categories, and themes were translated from Creole to English and back translated to Creole. The results of both Creole and English analysis were compared. When there

was a discrepancy the original transcripts in Creole were reviewed until consensus was derived. The final results were reviewed by a panel of investigators who were clinicians at GHESKIO and thus were familiar with the care of patients living with HIV. This panel also included bilingual researchers with expertise in qualitative research.

RESULTS

Data saturation was reached at 25 participants. 64% were women which represents the feminization of HIV in Haiti. The length of time on antiretroviral treatment ranged from 10 to 12 years. Interviews resulted in 681 codes have been grouped into 6 categories that best illustrate factors that enabled them to survive. The most frequently cited categories that illustrated factors that enabled participants to survive was the role of providers, the role of spirituality and their faith, the role of caring for children, having a goal, having a positive outlook, and medication adherence.

The Role of Providers:

"Then someone told me to come here. They told me that they will take good care of me here. They also told me they will not give me the medications all of the sudden without being tested. Then when I came to do the test they told me that I tested positive for HIV"

"Since I started to come here, everybody here has become my friend. I come here because everyone in the staff is my friend, because of my familiarity with my doctors, my familiarity with my nurses.

"My friend, I can tell you if Doctors did not exist, the country itself would disappear. I can say that the doctors come right after GOD"

Spirituality:

A major recurring category was that of spirituality and faith in God. God was viewed as a confidante, friend, and healer. Having God to confide in was essential for some participants who felt that they were unable to disclose their status to anyone else.

"*My problem is that I was stressed because I could not find a person who could understand me to share this with. And I realized that if I tell someone about my status that person will share it with others. Then I said to God that everything is in your in hands, please take over, don't let me get stressed too much"*

"I hope that God will make the cure available, as the treatment is now available to improve our health. Then God does his job, to make the cure available to us in order to keep living"

"The same way he let the disease enter my body; if he wants he can make it disappear. If he wants to let you suffer because of your sin he can let this happen, but since he is different from us he can treat us as well"

Belonging to a church reinforced the role of spirituality that the participant described. The church provided social support.

"I have been to church more than when I did not know I was infected. I have noticed that God deserves more glory because I was already in the tomb and he has withdrawn me. It is like your father that told you not to do something you do it and he still loves you and forgets you. So you have to be ashamed about your attitude and change! So I have to become wiser and more obedient towards God! "

"Even if I do not go to church I have to pray, but when you go to church and you have a place where you are praising the Lord it is better and you can even find prayer support. My prayer is too weak, I think if several people were praying God for my treatment I would have already found a solution."

The Role of Providing for One's Child:

Approximately 60% of the participants were women and many had young children at their time of diagnosis. Having children and supporting their children was another factor which enabled some to survive.

"Well (my kids), that's a great accomplishment for me, because I didn't expect that. The reason I didn't expect it. Because when you are working to pay school tuition for your child and the child really understand what you're doing for him, he understand the importance of education and completed high school, that is a great accomplishment for his parents"

"The thing that I'm proud of is the fact of my daughter goes to university now. I prayed God for that. I want her to be married before my death. I want God to keep me alive for that"

"*I just wanted to live, because I didn't want to die letting my children. Who would take care of them? I don't know. They wouldn't be educated*. "

Having a Goal:

Having a goal for economic development was also a crucial factor. For some participants, it was a process of acquiring skills for a profession in order to have an income that was empowering.

"I compare myself like other because I am doing all my activities. There is no difference between us. I only know that I am living with the virus but that does not mean that I am sick. I can say that I am like any other young person. Everything that they can do I can do it also"

"I am an educator, I inform the youth, I accompany them, and I show them that they are not alone. I work alongside them, and I support them"

"If for some reason I cannot do the laundry then I try to sell a few things out of my store. Also sewing is one of my daily activities as usual. I respect my dignity as long as I find something to do I will always try my hardest"

"For me, I want to complete my secondary studies, find a scholarship and to go study medicine, and become a pediatrician"

Positive Coping and Stress Reduction:

Another important aspect of survival was finding a way to cope with stress for dealing with HIV.

"Sometimes I give them jokes. I resigned on myself by giving jokes. That is how I confront life, in order to prevent stress getting me down"

"The most important thing consists in living with the disease like you used to live before you knew you were infected. Even if people are criticizing you, act as if nothing happened."

"Sometime, I don't even talk about the disease. I remember that I'm sick only when I come here."

"I was born with the disease and I know that everybody has their cross to lift in life. And I sometime say if I was not infected and I was handicapped or blind or if I had cancer and If I had to choose I would prefer being infected by the virus, because I can lift this cross but the other ones would be too heavy for me, when I imagine a person who is born but who cannot ever walk I consider Aids like a blessing compared to those diseases"

Attitudes Towards Medication Adherence:

Having a positive attitude toward medication adherence was also described as an essential aspect of living with HIV.

"I take my medicine as if I was taking vitamins. I just take the paper in which I have the medicine and I take it. I may hide the bottle to avoid people of reading what is written on the bottle. But I don't mind to just buy water and take my pills, I don't care." "I know I cannot spend one day without brushing my teeth so I have to do the same when it comes to taking the medicine, it is a must for me like brushing my teeth"

"When I do not take the medicine, I feel upset, nervous, stressed, I feel I have one day missing in my life. The medicine becomes a drug for me. I mean I cannot do anything without it."

Theory:

In order to survive, one had to look past the disease and have another meaning to their lives. The concept is outlined in **Figure 2.1**.

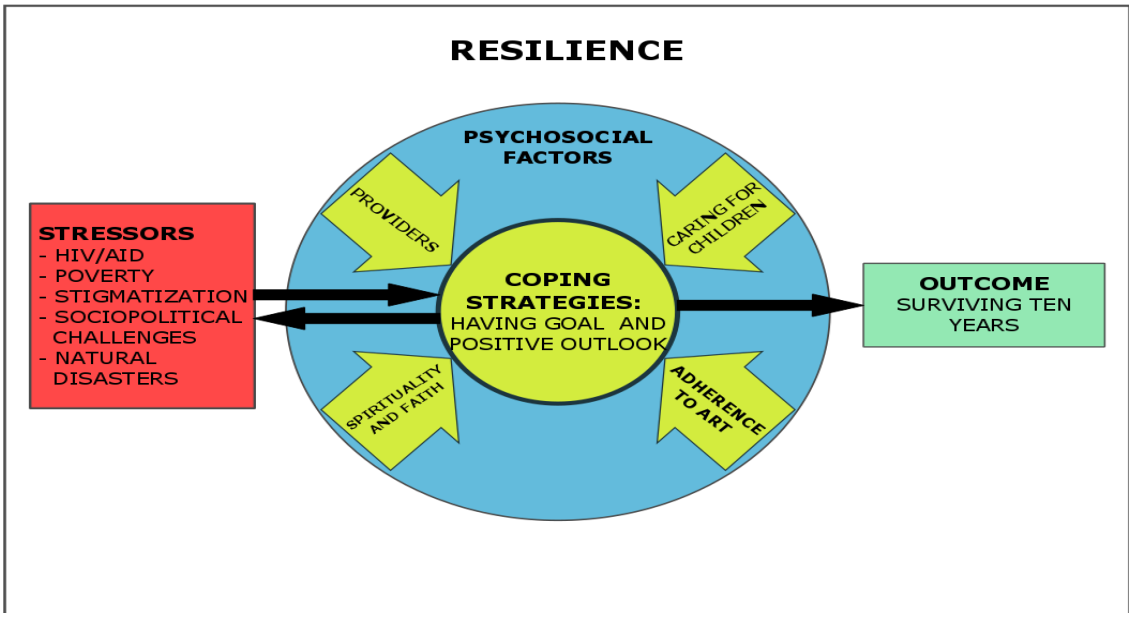

Figure 2.1 Elements of resilience of the ten year AIDS survivors at GHESKIO

DISCUSSION

The impact of HIV on the lives of Haitian patients is well-known. However, what is less known, is how patients have been able to survive a disease that has been until recent decades, invariably fatal. This paper is a paradigm shift in the approach to studying HIV. The premise of this paper is that understanding factors that enable survival is important to developing sustainable programs.

This qualitative study identified 6 factors: the role of providers, the role of spirituality and their faith, the role of caring for children, having a goal, having a positive outlook, and medication adherence. The underlying theme was having something to live for and something to sustain life. There are prior reports by Severe et al. of the resilience of the people of Haiti that pointed the will to survive in spite of their circumstances. For many participants in this study factors such as spirituality and one's child took precedence over the disease. These factors enabled patients to transcend their reality and thus, survive.

An overarching theory that can best describe this phenomenon of survival was that one had to look past the disease and have another meaning in life. As an example, faith provided a sense of hope and healing that surpassed participants' realities. Having children who needed to be reared and educated enabled patients to transcend their current circumstances and live towards a goal of providing for children. Having personal goals, such as the desire to work, enabled patients to live beyond their circumstances and seeming overcome the despair of HIV. Having support from providers and other family also enabled patients to survive and reinforced their reason for living. Even their attitude toward taking medications was seemed to defy their circumstances. Patients described taking medications like vitamins or routine as brushing one's teeth.

Although there were descriptions of the devastating health impacts of HIV itself, there was an underlying current of resilience, hope, and the desire to live. This study has limitations in that it was done among patient from one practice site and there was a preponderance of women. However, reflects the reality that few clinical sites are able to provide care and support research like GHESKIO. This study also reflects the feminization of HIV in Haiti. The sample size of 25 is consistent with prior qualitative studies. Additionally, it is not known whether those who survived and those who did not had different outlooks. One can only conclude that these results are illustrations of what some participants who survived described. Comparison with those who did not survive cannot be made.

Qualitative studies provide an important adjunct to the traditional cohort studies or clinical trials. The cross-language approach provides guidance on future studies conducted in participants own language. This is critically important to preserving the essence of what participants are reporting and ensuring that the meaning is not lost in translation. The success of GHESKIOs ART program demonstrates that rapid and wide-scale implementation of ART is feasible. The findings from 910 patients provide rationale for replication of this program and the return on investment on supporting ART treatment in resource poor countries. Moreover, this study demonstrates the importance of developing supportive programs that help to build resilience and hope. The large proportion of women who have low education in Haiti does not necessarily equate with a lack of goals. As described in this study, women with children wanted to work and support of their children's education. Women voiced their desire in working any job type, such as doing laundry.

This study provides a portrait of Haiti that is not defined by death or hopelessness. Understanding the concept of survival among this population can help to advance studies from mortality to survival and quality of life.

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